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EXAMINER
ULM, JOHN D

ART UNIT	PAPER NUMBER
1646	23

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/333,966	Applicant(s) Yu et al.
	Examiner John Ulm	Art Unit 1646

-- ***The MAILING DATE of this communication appears on the cover sheet with the correspondence address*** --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) X Responsive to communication(s) filed on *Jul 30, 2002* .

2a) ☐ This action is **FINAL**. 2b) X This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) X Claim(s) *27-75* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) X Claim(s) *27-75* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐	Notice of References Cited (PTO-892)	4) ☐	Interview Summary (PTO-413) Paper No(s).
2) ☐	Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) ☐	Notice of Informal Patent Application (PTO-152)
3) ☐	Information Disclosure Statement(s) (PTO-1449) Paper No(s).	6) ☐	Other:

1) Claims 27 to 75 are pending in the instant application. Claims 47 to 75 have been added as requested by Applicant in Paper Number 22, filed 30 July of 2002.

2) Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

3) The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4) A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 30 July of 2002 has been entered.

5) Claims 37 to 75 are generic to a plurality of disclosed patentably distinct species of polypeptide fragment of SEQ ID NO:2. Applicant is required under 35 U.S.C. 121 to elect a single disclosed species of peptide fragment, even though this requirement is traversed.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

6) Claim 64 is objected to as reciting an improper Markush Group. M.P.E.P. 803.02 states that:

> "Since the decisions in In re Weber **,198 USPQ 328 (CCPA 1978); and In re Haas, 198 USPQ 334 (CCPA 1978), it is improper for the Office to refuse to examine that which applicants regard as their invention, unless the subject matter in a claim lacks unity of invention, In re Harnish , 631 F.2d 716, 206 USPQ 300 (CCPA 1980); Ex Parte Hozumi , 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984). Broadly, unity of invention exists where compounds included within a Markush group (1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility."

The different sequences recited in claim 64 are 8 chemically unrelated peptide structures which lack a common utility which is based upon a shared structural feature.

7) Claims 27 to 75 rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, substantial and specific asserted utility or a well established utility for those reasons of record applied to claims 27 to 46 in section 2 of Paper Number 5, section 5 of Paper Number 16 and section 4 of Paper Number 19.

Applicant has traversed this rejection on the basis that a polypeptide of the instant invention can be used to "generate" specific agonists thereto and that those agonists can be used "to treat a disease wherein decreased apoptosis is exhibited". Applicant further identifies autoimmune diseases as a class of disorder which can be treated by the administration of an agonist of the claimed polypeptide and essentially argues that the instant specification would lead one of ordinary skill to produce agonistic antibodies to a receptor of the instant invention and to

employ those antibodies to induce T-cell apoptosis in individuals suffering from an auto-immune disease. These arguments were answered at length in section 4 of Paper Number 19.

Applicant has asserted that the Tartaglia et al. publication (J. Biol. Chem. 267:4304-4307, 1992) and the Wang et al. publication (Mol. and Cellu. Biol. 21:3451-3461, 2001), as well as a poster identified by Applicant, support the conclusions that agonist antibodies to the claimed protein can activate it and that those antibodies have clinical utility. Applicant is advised that the poster they have referred to has not been considered because the font size of the copy provided as Exhibit C of Paper Number 22 is of such small size as to render it illegible and because the date at which time the information presented therein became available to the public has not been provided.

It is unclear why Applicant has cited the Wang et al. publication, which appears to be silent on the subject of agonistic antibodies to a "DR3" protein or the clinical administration of agonist antibodies to any receptor protein.

The Tartaglia et al. publication describes the production of agonistic antibodies to a TNF receptor. It does not avoid the instant rejection because the ability of an artisan to produce agonistic antibodies to a receptor comprising only a single transmembrane domain has never been disputed. In fact, it is asserted that the production of agonistic monoclonal antibodies to receptors comprising only a single transmembrane domain, such as the receptor tyrosine kinases and members of the TNF receptor family, was a routine practice in the art prior to the making of the instant invention. The instant rejection is based upon the premise that there is not a single

reference of record describing the effective clinical administration of an agonistic antibody to an individual prior to the filing of the instant application.

Applicant urges that clinical data is not required to support an assertion of clinical utility. This is true. Applicant does not need to provide clinical evidence that agonistic antibodies to DR3 are effective in achieving a desired response **if** there is be some reasonably predictive correlation between the experimental data presented in the instant specification and the clinically proven efficacy of analogous compounds (see *In re Brana*, 51 F.3d 1560,1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995). Applicant has not been required to provide clinical data with respect to the application of DR3 agonistic antibodies. Applicant has merely been required to establish that such antibodies would reasonably be expected to have clinical utility based upon the established clinical utility of agonistic antibodies in general, and Applicant has failed to establish this critical nexus in support of their alleged utility.

Applicant argues that an effective chemotherapeutic agent need not be selective. Applicant's arguments are fundamentally wrong. All chemotherapeutic agents are selective to some extent. Whereas most chemotherapeutic agents may have some toxicity for cells and tissues which are not the target of their application, they are still selective. Otherwise, those agent would kill the host as readily as they kill the target cells. Cancer cells are very easy to kill. One can simply heat them or pour table salt or distilled water on them. To kill the cancerous cells in an organism merely requires one to incinerate that organism. The cancer cells will certainly be killed by this action, as will any infectious parasites as well as any undesired bacteria or viruses which

might be present in that organism. Therefore, any clinically useful agent must selectively kill an undesired cell, organism or virus without killing the individual being treated. Even when administering a dose of radiation sufficient to destroy the stem cells in a leukemia patient, the agent is selective because one does not destroy all of that patient's cells. Agonist antibodies to DR3 do not have practical utility in currently available form because instant application does not explain the practical advantage of killing all of the T-cells in an organism, nor does it disclose a process of employing a protein of the instant invention, or an agonist thereto, to destroy an undesired population of T-cells to the exclusion of a desired population.

The most relevant publication cited by Applicant in traversal of the instant rejection is the Migone et al. publication (Immunity 16:479-492, 2002). This reference, which was published after the filing of the instant application, clearly shows that the instant specification is fatally defective. The text on page 5 of the instant specification appears to imply that the receptor protein of the instant specification is "involved in the deletion of peripheral T lymphocytes of the immune system". Page 6 of the instant specification expressly teaches that the administration of a DR3 agonist to a cell expressing DR3 will kill that cell. It further teaches that the administration of a DR3 antagonist to that same cell will inhibit cell death from exposure to a DR3 agonist. These predictions were made in the complete absence of a knowledge of the identity of a native ligand for DR3 or of the physiological effects of that ligand upon T-cells. In contrast with the teachings of the instant specification, the Migone et al. publication provides experimental evidence that the administration of the DR3 agonist TL1A to resting T-cells has no detectable effect upon

those cells and that the administration of TL1A to activated T-cells **induces them to proliferate**. The "discussion" section of this publication expressly states that "[w]e have found that TL1A functions specifically as a T cell costimmulator, which is consistent with DR3 being mainly expressed on activated T cell." Therefore, one can not use a DR3 protein of the instant invention to identify agonists which induce T-cell death or antagonist that inhibit T cell death, as disclosed in the instant specification, because Applicant's speculative conclusions about the natural role of DR3 were wrong. The only cells naturally producing DR3 which were killed by a DR3 agonist were of the tumor cell line TF-1, and then "only when protein synthesis is blocked and proliferative signals are inhibited".

8) Claims 27 to 75 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, substantial and specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

9) Claims 27 to 46 stand rejected under 35 U.S.C. 102(b) as being clearly anticipated by each of the Chinnaiyan et al. (SCIENCE 274:990-992, 08 Nov. 1996, of record) and Kitson et al. (NATURE 384:372-375, 28 Nov. 1996, of record) for those reasons if record in section 7 of Paper Number 16.

10) Applicant's arguments filed 30 July of 2002 have been fully considered but they are not persuasive.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John D. Ulm whose telephone number is (703) 308-4008. The examiner can normally be reached on Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242 or (703) 872-9306. Official responses under 37 C.F.R. § 1.116 should be directed to (703) 872-9307.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.